Epidemiology

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Overview of Epidemiology Issues

- EPA's draft IRIS conclusions
  - All leukemias
  - Myeloid leukemias
- The NRC report and its criticisms
- Standard methods for critical review and synthesis of epidemiological evidence
- Recent critical review (Checkoway, Boffetta, et al., 2012)

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EPA – IRIS Conclusion: All leukemia

"While the epidemiologic evidence for a causal association between formaldehyde and all leukemia as a group is not at strong as for all LHP as a group, the repeated identification of an association in multiple meta-analyses taken together with the clear causal association between myeloid leukemia demonstrated by Hauptmann et al. (2009) and the consistent evidence reported by Beane Freeman et al. (2009) are sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all leukemia as a group."

Draft IRIS Review – page 4-182

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EPA – IRIS Conclusion: Myeloid leukemia

"Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann et al., 2009; Pinkerton at al., 2003; Hayes et al., 1990; Stroup et al., 1986; Walrath and Fraumeni, 1984, Walrath and Fraumeni, 1983; but not Beane Freeman et al., 2009), the statistically significant meta analysis by Zhang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia."

Draft IRIS Review – page 4-184/5

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NRC Report

- Released in April 2011
- Criticized Draft IRIS Report methods:
  - Lack of transparency in EPA review process
  - Failure to evaluate strengths and weaknesses
  - "Lumping" in causal conclusions of all lymphohematopoeitic (LHP) malignancies and other subsets of different cancers
  - Ignoring exposure metrics and the fact that exposure measurements are lacking in most of the epidemiology studies

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Standard Methods for Review and Synthesis of Epidemiological Evidence

- Clearly describe how literature was identified and selected
- State criteria used to determine study quality and "weighting" of study evidence
- Assess strengths and weaknesses of "key" studies
  - Address major types of bias, sample size,
  - Quality of exposure measures
- Provide tables summarizing evidence

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Recent Critical Review

- Checkoway, Boffetta et al., 2012, "Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other LHP malignancies"
- Forest plots: leukemias, myeloid leukemia, chronic lymphocytic leukemia, lymphomas and non-Hodgkin lymphoma
- Lack of exposure data for most studies, exception: Beane Freeman
- The evidence as presented:

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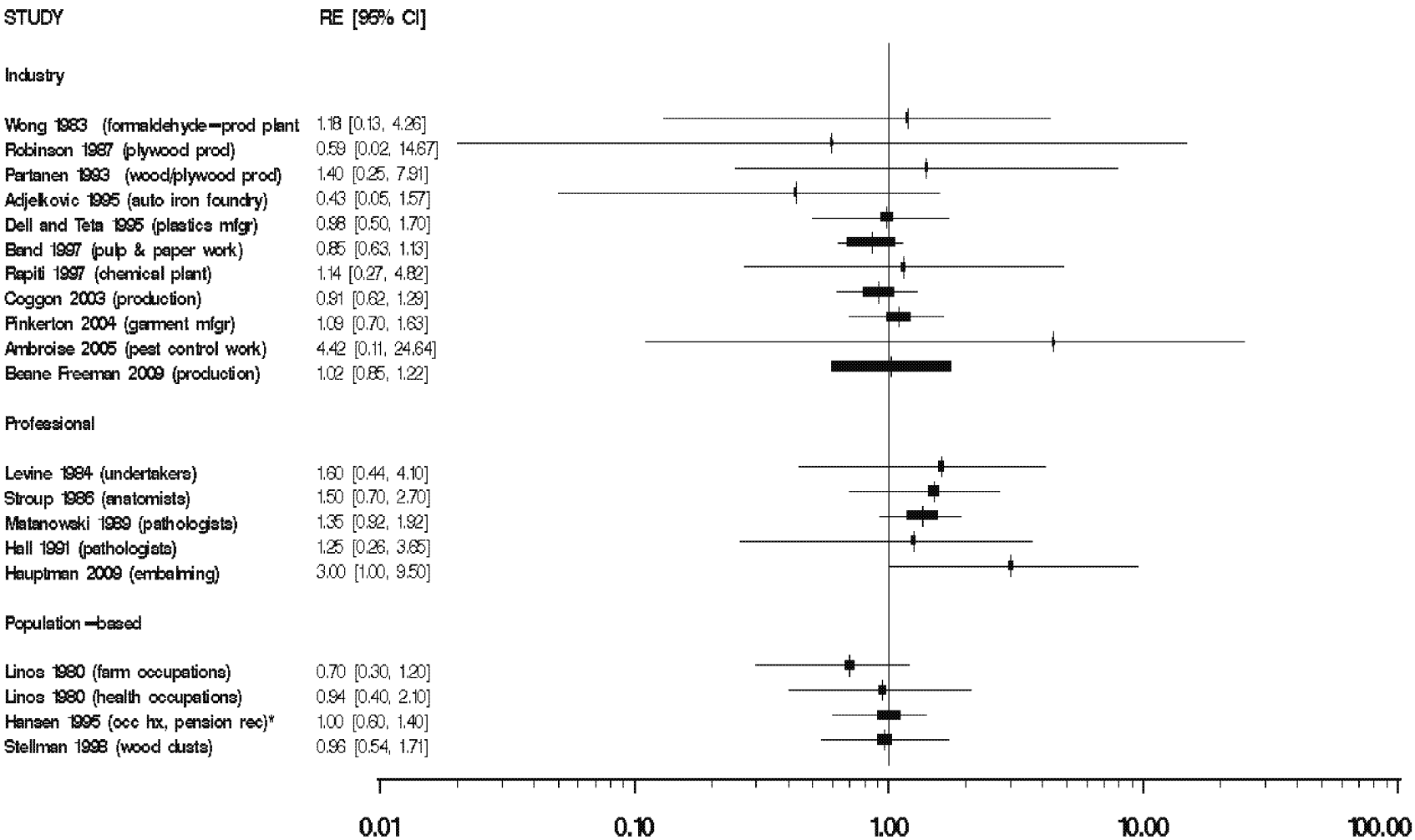
Figure 1 Forest plot of formaldehyde exposure and leukemias



*Formaldehyde exposure estimated from questionnaires or occupational history records.

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Figure 2 Forest plot of formaldehyde exposure and myeloid leukemia

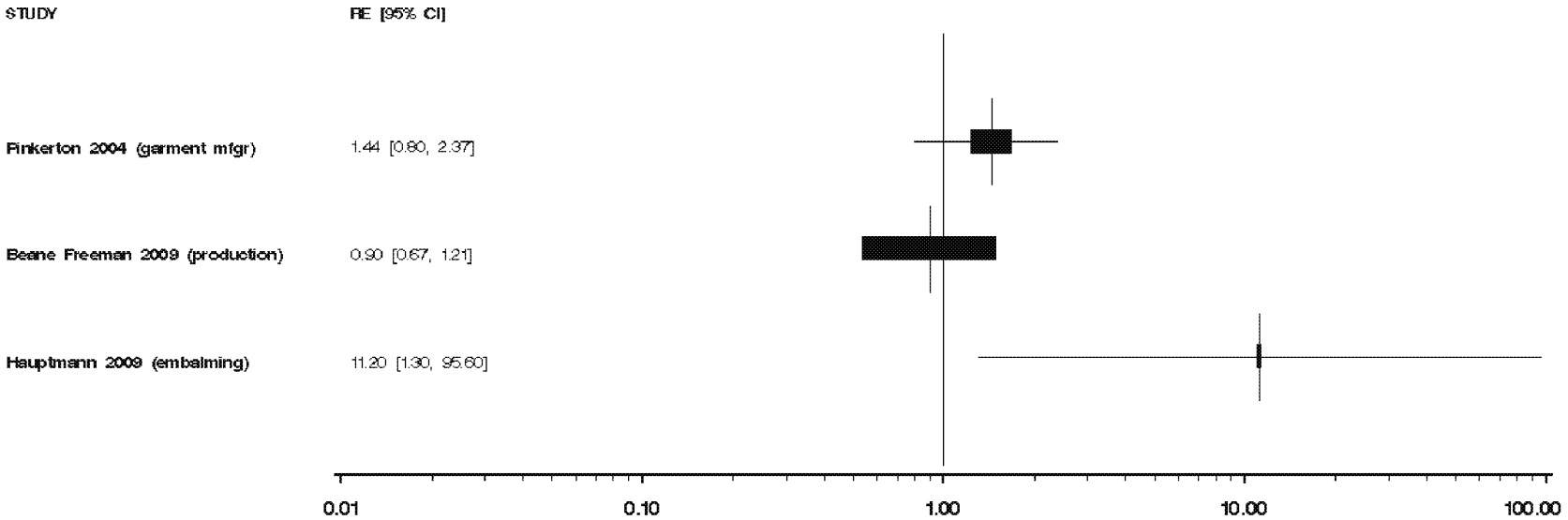

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Figure 3 Forest plot of formaldehyde exposure and chronic lymphocytic leukemia

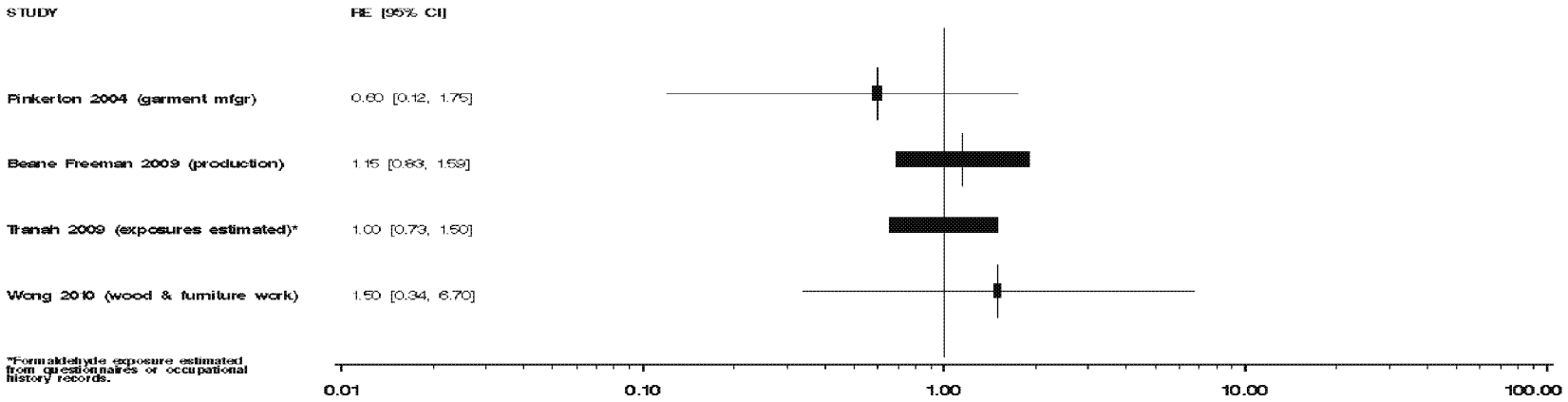

Figure 4 Forest plot of formaldehyde exposure and lymphomas

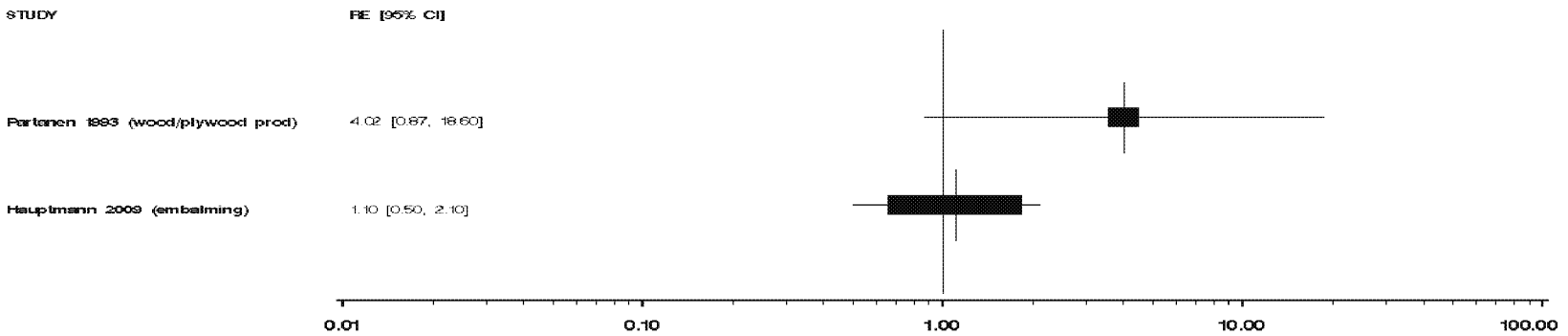

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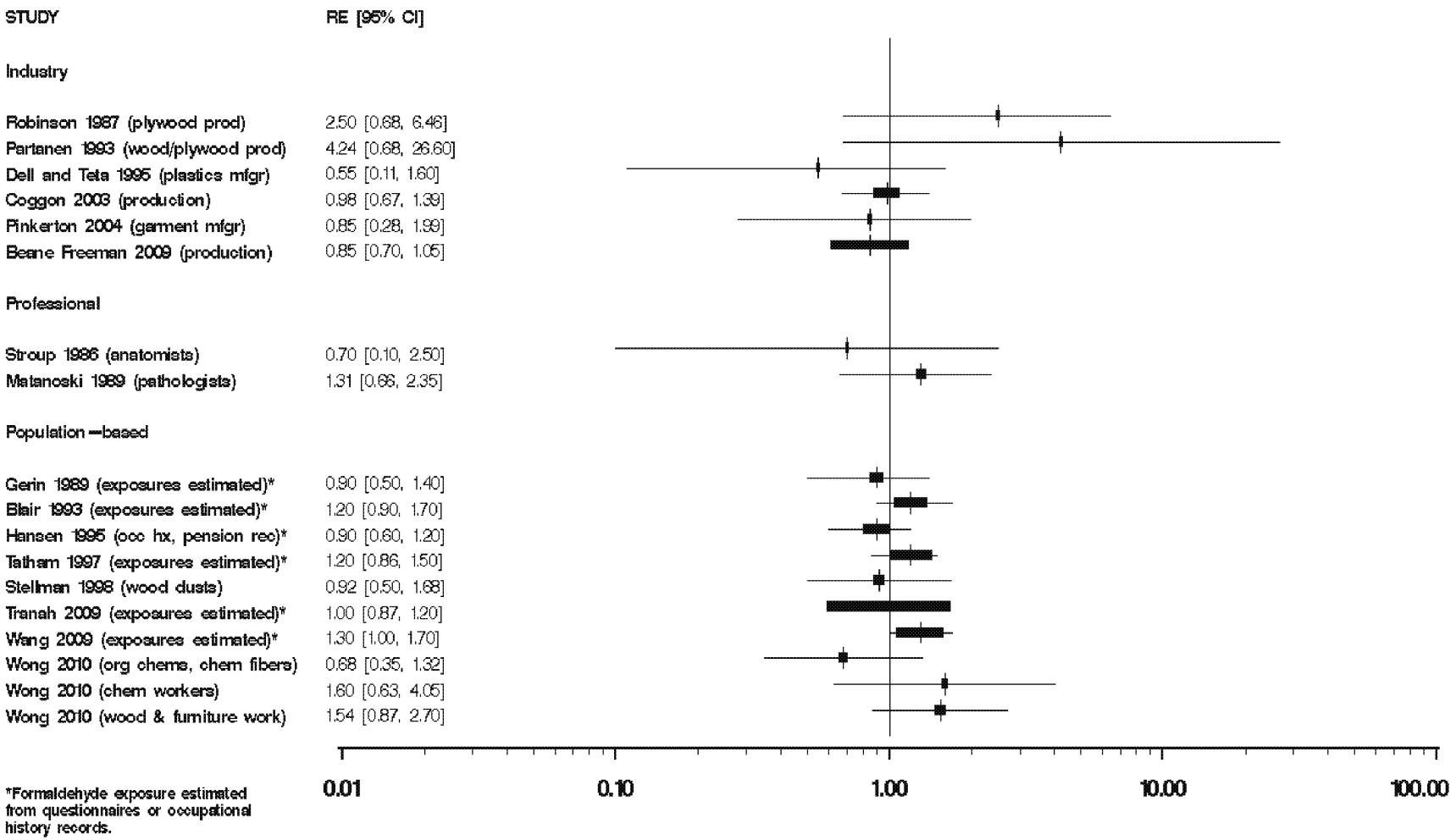
Figure 5 Forest plot of formaldehyde exposure and non–Hodgkin lymphoma



*Formaldehyde exposure estimated from questionnaires or occupational history records.

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Conclusion:

"At present, there is no consistent or strong epidemiologic evidence that formaldehyde is causally related to any of the LHM."

Checkoway, Boffetta, et al., 2012.

Does Formaldehyde Cause Nasopharyngeal Cancer (NPC)?

- Epidemiological evidence is inconsistent
  - Does *not* generally support a causal connection
  - Limited to an excess of NPC cases in a single plant in the NCI study
- The evidence as presented (Bachand, 2010):

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Forest Plot for NPC Study Data

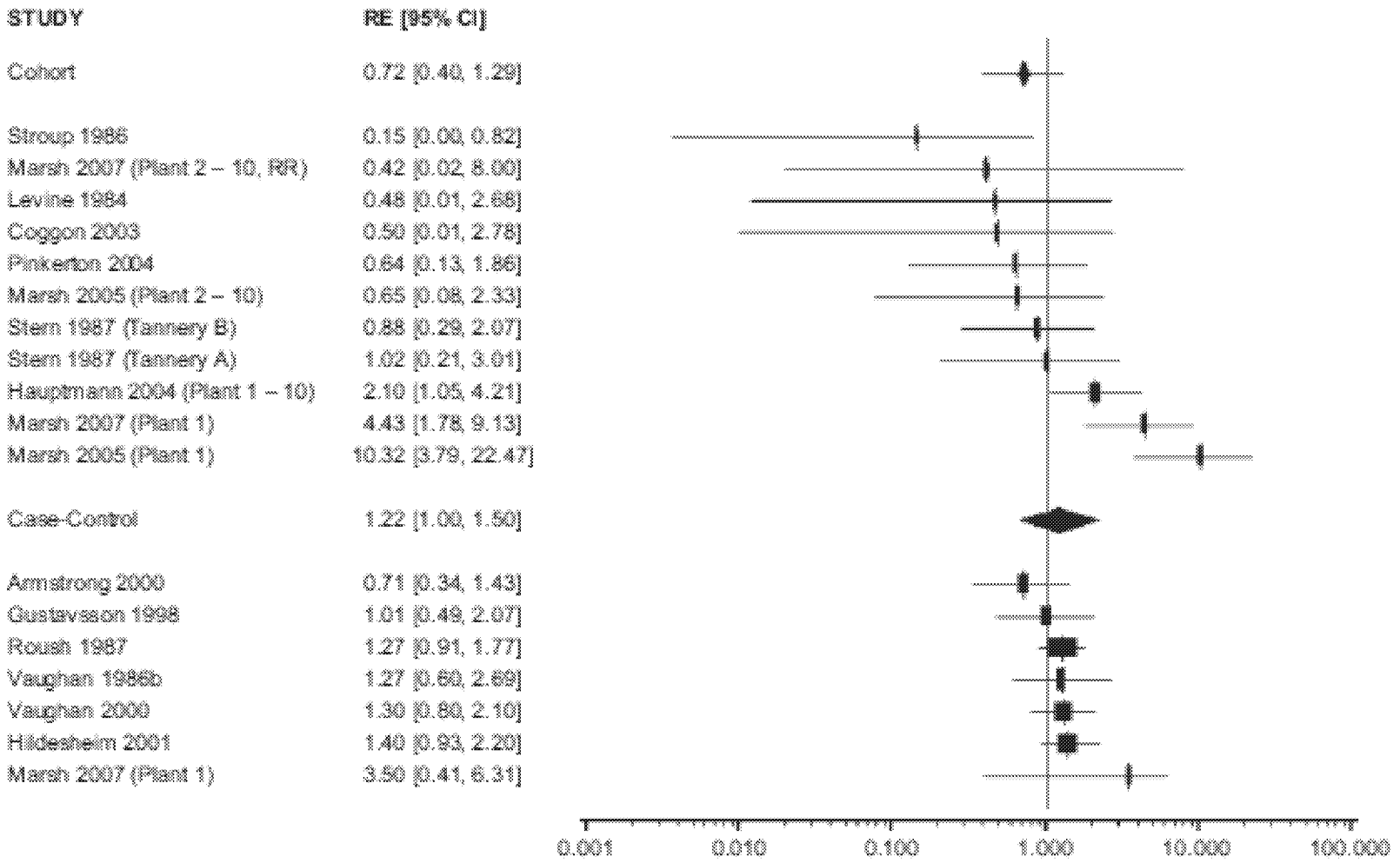

Figure 4. Forest plot by study design for nasopharyngeal cancer.

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Nasopharyngeal Cancer

- Epidemiological evidence from cohort and case-control studies is inconsistent. Does *not* generally support a causal connection between formaldehyde exposure and nasopharyngeal cancer.

- Epidemiological evidence is limited to an excess of nasopharyngeal cancers in one plant included in the NCI cohort study (Blair et al. 1986; Hauptmann et al. 2004).

- Nine other plants in this cohort, two other large cohort studies (Coggin et al. 2003; Pinkerton et al. 2004), and several smaller cohort studies do provide *no* evidence for increased risk.

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Epidemiological Basis for Causal Conclusions

- With few exceptions, the epidemiological literature on formaldehyde exposure and leukemia risks consistently demonstrates
  - No statistically significant risks among exposed workers;
  - No consistent associations with various exposure metrics
- Similarly, the epidemiological literature on NPC risk demonstrates little consistency and largely has been driven by an NPC cluster at a single facility
- Critical review and strength of evidence evaluation fails to support causal associations between formaldehyde and these diseases

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